

## **REMARKS**

### **I.     Status of the Claims**

Claims 1-14 are pending in the application, and claims 2 and 12 stand withdrawn pursuant to a restriction requirement. Thus, claims 1, 3-11, 13 and 14 are under consideration and stand rejected under 35 U.S.C. §112, second paragraph and 35 U.S.C. §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

### **II.    Rejections Under 35 U.S.C. §112, Second Paragraph**

Claims 1, 3-11, 13 and 14 stand rejected under the second paragraph of §112 as indefinite.

Claims 1, 5 and 7 are rejected for inclusion of parenthetical's. Applicants have amended claims 1 and 7 to remove the parentheticals, but applicants are unable to identify any parentheticals in claim 5.

Claim 3 is rejected as referring to features (c) and (d) whereas claim 1, from which claim 3 depends, mentions only features (a) and (b). Applicants have amended claim 3 to now refer to claim 2. As such, it is believed that claim 3 may be considered withdrawn.

Claims 7 and 11 are rejected for use of the optional language "such as." Applicants have amended to the claims to remove this language and, where appropriate, added further dependent claims.

Claims 13 is rejected for inclusion of "preferred" or "in particular" language. Amendments have been provided to remove the rejected language.

Reconsideration and withdrawal of the rejections is therefore respectfully requested.

### **III. Rejection Under 35 U.S.C. §103**

Claims 1, 4, 5, 7-11, 13 and 14 stand rejected under §103 as obvious over Adjei (“the ‘294 patent”) in view of Kotitschke (“the ‘264 patent”). The ‘294 patent is cited for teaching stabilization of pharmaceutical formulations by selecting from a long list of stabilizing agents such as natural and modified amino acids. The ‘264 patent is cited as disclosure a process of sterilizing a factor VIII pharmaceutical formulation using tenside. Thus, because the examiner equates the stabilization methods of the ‘294 patent with those claimed here, the mere selection of factor VIII, in light of the ‘264 patent, is considered obvious.

In making this argument, the examiner turns to the *KSR* decision to argue that “mere differences” are insufficient to establish nonobviousness, and that the person of ordinary skill in the art can “fit the teachings of multiple patents together.” However, neither of these alleged holdings helps the rejection here. As stated above, the combination of the ‘264 patent with the ‘294 can do no more than indicate that Factor VIII was worth formulating – it cannot correct the defects of the ‘294 patent. Moreover, the examiner has failed to address all of the differences between the ‘294 patent and the presently claimed methods, as set out below. Therefore, applicants traverse.

The present claims relate to a composition to stabilize proteins in pharmaceuticals, which composition is characterized by four technical features: (a) it comprises a surfactant; (b) it comprises at least Glu + Gln or Asp + Asn; (c) it does not comprise human serum albumin (nor any other non-human serum albumin); and (d) it stabilizes proteins.

The ‘294 patent discloses a suspension aerosol formulation comprising a medicament, a propellant, and a stabilizer. Admittedly, the medicament may be a protein (column 2, lines 13/20). However, the medicaments that have been exemplified in the ‘294 patent are, without

exception, small molecules, and not a single protein is listed in the paragraph spanning lines 21/39 in column 2 (the same holds through for claims 3, 17, 24, 25, and 26). Although the patent discloses amino acids including most, if not all, of the naturally-occurring amino acids (column 3, lines 15-47, claims 2, 15, and 23) as stabilizers, the patent does *not* disclose a pairwise utilization of Glu + Gln or Asp + Asn. The '294 patent in fact discloses the optional utilization of a surfactant, although the stability of the suspension aerosol formulation is asserted to be also achieved without the addition of a surfactant (column 4, lines 10-12). Finally, the '294 patent does not disclose that one can forego human serum albumin as a stabilizing agent for the protein medicament.

From the foregoing, it is evident that the teaching of the '294 patent is quite distinct from the subject-matter claimed. That is, that the '294 patent discloses a stable suspension aerosol formulation comprising a small molecule as a pharmaceutical, a propellant, any amino acid as a stabilizing agent, and a surfactant as an additional but optional ingredient. It does *not* teach, however, the stabilization of proteins, let alone a stabilization of proteins by Glu/Gln or Asp/Asn and a surfactant in the absence of human serum albumin.

Quiet conversely, the '264 patent discloses a process to sterilize a factor VIII preparation. Sterilization means to provide a factor VIII preparation that is free of hepatitis virus. In order to sterilize the factor VIII preparation, it is treated with a surfactant, subjected to UV light, treated with beta-propiolactone, and treated with colloidal silica. Stabilization is not obtained, but factor VIII activity is lost (*e.g.*, column 4, lines 63/68, column 5, lines 1/18), *which is in fact the opposite of protein stabilization*. Thus, the '264 can *only* be useful for the general notion that factor VIII may be used in a pharmaceutical composition. Thus, it *cannot* be used to augment any other shortcoming of the primary reference.

The question, then, is whether the specific selection of Glu + Gln or Asp + Asn would be considered nonobvious over the teachings of the '294 patent, and if not, whether the further recitation of no human serum albumin would nonetheless render the claims nonobvious. Returning to the *KSR* decision, the relevant inquiry would seem not to be that offered by the examiner, but instead, whether there was sufficient direction in the '294 patent's teachings to arrive at the particular features of the presently claimed invention. Even a relaxed post-*KSR* standard for suggestion in the art, there must be *some* teaching of each element of the claimed invention *somewhere*. See *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) (emphasis added) (to establish *prima facie* obviousness of a claimed invention, all the claim features must be taught or suggested by the prior art). Indeed, as the Board of Patent Appeal and Interferences has recently confirmed, a proper obviousness determination requires that an examiner make "a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art." See *In re Wada and Murphy*, Appeal 2007-3733, citing *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis in original).

Further, the necessary presence of all claim features is axiomatic, since the Supreme Court has long held that obviousness is a question of law based on underlying factual inquiries, including ... ascertaining the differences between *the claimed invention* and the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) (emphasis added). Indeed, Applicant submits that this is why MPEP §904 instructs examiners to conduct an art search that covers "the invention *as described and claimed*." (emphasis added). Lastly, Applicant respectfully directs attention to MPEP § 2143, which buttresses the conclusion that obviousness requires at least a suggestion of all of the features of a claim, since the Supreme Court in *KSR Int'l v. Teleflex Inc.* stated that "there must be some articulated reasoning with some rational

underpinning to support the legal conclusion of obviousness.” *KSR Int’l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

By the examiner’s own admission, the ‘294 patent provides a laundry list of **at least** 32 stabilizing agents from which one or more could be selected for use in the disclosed methods. Even if one were to limit that inquiry to enumeration of only **two** such agents, as in the present claims, the number of possibilities would be **at least** 992 (32 x 31). Selecting 2 out of almost one thousand choices is hardly the kind of situation identified in *KSR* “where one skilled in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.”

Even more clear is that fact that the prior art fails in teaching that human serum albumin is permissibly omitted from a protein composition when these particular amino acids are selected. The prior art is completely silent on this feature, and it is completely unpredictable from this art that such could be accomplished with **any** selection made from the ‘294 patent, much less the selection of these two amino acid pairs.

In sum, one can only support a conclusion obviousness when all the claimed elements **were known in the prior art**, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. *KSR*, 82 USPQ2d at 1395; *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950). If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

Here, there is little doubt that the cited art fails both in providing the necessary guidance to select the features of the present claims (Glu + Gln or Asp + Asn), and also fails in providing a reasonable likelihood of success in achieving the results (no human serum albumin needed). As such, no *prima facie* case has been established. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

#### IV. Conclusions

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding the content of this responses, a telephone call to the undersigned is invited.

Respectfully submitted,



Steven L. Highlander  
Reg. No. 37,642  
Attorney for  
Jurgen Frevert

FULBRIGHT & JAWORSKI L.L.P.  
600 Congress Avenue, Suite 2400  
Austin, Texas 78701  
(512) 536-3184

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